Right and left ventricular function at rest and with exercise after the Mustard operation for transposition of the great arteries

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SUMMARY Right and left ventricular function was assessed in 25 children (mean age at study 12·2 years and at operation 2·6 years) after a Mustard repair for transposition of the great arteries. Gated first pass and gated equilibrium radionuclide ventriculography was performed on all patients at rest and during supine bicycle exercise. The mean right ventricular ejection fraction did not increase with exercise by either technique. Individual results for right ventricular ejection fraction showed that with the gated equilibrium technique 71% had an abnormal exercise response (normal response being an increase in ejection fraction >5%) and with the gated first pass technique 61% had abnormal results. Although the mean left ventricular ejection fraction increased significantly with exercise, 35% of patients had an abnormal exercise response with the equilibrium technique and 41% with the first pass technique. There was no evidence of a predictive relation between ventricular function and any clinical or haemodynamic variable examined. Covert right and left ventricular dysfunction can frequently be detected by exercise radionuclide ventriculography in long term survivors of repair for transposition of the great arteries. The prognostic consequences of these findings are unclear at present.

As there has been a notable reduction in the incidence of the major technical surgical problems of the baffle operation for transposition of the great arteries, attention is now being focused on the long term survivors, particularly with regard to right ventricular dysfunction. This has been detected at rest by contrast angiography[1][2] and by echocardiography.[3] Radionuclide ventriculography is a less invasive method of determining ventricular function than contrast angiography and has the advantage of being able to assess functional ventricular reserve with the stress of exercise.[4] This study was therefore carried out to determine right and left ventricular function in long term survivors of the Mustard operation by radionuclide ventriculography at rest and during supine bicycle exercise. Clinical and haemodynamic variables

were also measured to determine any possible relation with ventricular function.

Patients and methods

STUDY POPULATION

All 25 children in this study had Mustard repairs performed for transposition of the great arteries between February 1971 and November 1974. All were followed by the department of cardiology at the Royal Children's Hospital, Melbourne. Children with appreciable neurological or intellectual impairment, which would have precluded adequate performance or understanding of the study protocol, were excluded. A lower age limit of 9 years was dictated by the unsuitability of the available exercise equipment for smaller patients.

A full clinical assessment was performed, including chest radiography and an electrocardiogram. Eighteen of the children had technically satisfactory 24 hour ambulatory recordings. Details of original diagnosis and treatment, preoperative progress, and age at

operation were taken from patient records. Data from postoperative cardiac catheterisation, performed within two years of the original operation, were available for all patients. Subsequent progress including further operations and cardiac catheterisations was noted.

Thirteen patients were boys and 12 girls. Twenty three had no associated defects, one associated pulmonary stenosis, and one an associated ventricular septal defect. The mean age was 12·2 (range 9·3–16) years, and the mean number of years since operation was 10·9 (range 8–11·9) years. The mean age at operation was 2·2 (range 0·5–4·9) years.

Twenty four of the children were asymptomatic, although three were taking digoxin—two because of right ventricular dysfunction noted previously on angiography, and one because of supraventricular tachycardia—and one was taking verapamil for dynamic left ventricular outflow tract obstruction. The child who was symptomatic had chest pain with exercise, which was subsequently found to be due to ostial stenosis of the coronary sinus secondary to baffle repair.

Nine of the 25 children had significant superior vena caval obstruction (>3 mm Hg mean pressure difference between superior vena cava and systemic venous atrium[5]); none had symptoms related to obstruction. Five had sick sinus syndrome and six ventricular extrasystoles detected on 24 hour ambulatory electrocardiograms, although none had symptoms related to arrhythmias.

STUDY PROTOCOL
All children were studied at the nuclear medicine department of the Alfred Hospital, Melbourne, between August 1982 and March 1983. The aim of the study was explained to the parents and a detailed description was given to the children.

Continuous supine graded exercise was performed using an electronically braked bicycle ergometer (Siemens Elema). The initial starting workload was either 100 or 150 kpm/min (16·3 or 24·45 W) depending on patient size with an increase every four minutes by a further identical increment as tolerated until exhaustion. Blood pressure and heart rate were measured at rest, in the third minute of each workload, and at maximal exercise. A single electrocardiogram lead was monitored before, during, and for 10 minutes after exercise.

Right ventricular ejection fraction and left ventricular ejection fraction were measured at rest and during exercise using both the left anterior oblique electrocardiogram gated equilibrium technique[6] and the right anterior oblique electrocardiogram gated first pass technique.[7] This combined approach was possible by using a biplane collimator (Cardiac Medical Systems Corp, Northbrook, Ill) fitted to a low energy mobile small field of view scintillation gamma camera (Siemens, Des Plaines, Ill).

The modified in vivo labelled red blood cell technique was used.[8] The total dose of technetium 99m (based on an adult dose of 800 MBq (22·1 mCi), and stannous pyrophosphate was calculated according to the patient's weight.[9] An intravenous cannula (18–22 gauge) was inserted into the antecubital fossa. After the patient had been positioned and restrained with feet on the pedals and ready for exercise 1–2 ml of blood which had been labelled with one third of the total dose of technetium 99m was injected as a bolus for baseline first pass imaging using a 10 ml saline flush. For the right anterior oblique first pass images the collimator was positioned parallel to the anterior chest wall so that the right half of the biplane collimator gave an image angle of 30°. A small test injection of technetium 99m was given to help position the camera before the main bolus was injected. After first pass images had been taken the camera was angled to give the best separation of the right and left ventricles using the left anterior oblique view provided by the left half of the biplane collimator. Left anterior oblique equilibrium imaging was then performed for two minutes at rest and during the last two minutes of each four minute exercise workload. Immediately before exercise was stopped repeat first pass images were performed at maximal exercise using the remaining two thirds of the technetium 99m dose.

A PDP 11/34 dedicated minicomputer with Gamma 11 software (Digital Equipment Corporation, Maynard, Mass) was used to acquire data and analyse the results. The calculation of right and left ventricular ejection fractions used equilibrium[6] and first pass[7] techniques described previously for left ventricular ejection fractions. The gated first pass data were acquired using the physiological list mode of acquisition with subsequent reformatting of composite electrocardiogram gated cardiac cycles. First pass and equilibrium analyses of right ventricular ejection fraction were performed in a similar way to those described by Winzelberg *et al*[10] and Maddahi *et al*[11] respectively except that in each case a semiautomated method for defining the free edge of the ventricle[6] was used. In all cases the ejection fraction was calculated from the systolic decrease in net ventricular counts using separately defined end diastolic and end systolic regions of interest.

The lower limit of normal for resting left ventricular ejection fraction was defined as 55%[6] and for resting right ventricular ejection fraction as 45%.[12] [13] A normal ejection fraction response to exercise for both right[13] and left[13] [6] ventricles was defined as an increase of more then 5% from rest to maximal exercise or as a value >75% at both rest and exercise.

Table 1 *Mean (±SEM) haemodynamic values in 25 children*

	At rest	*After exercise*	*% Increase*
Heart rate (beats/min)	68±2	136±5	100%
Systolic blood pressure (mm Hg)	108±2	147±5	37%

STATISTICAL METHODS

Ejection fractions at rest and during maximal exercise were compared using a paired t test. The various clinical and haemodynamic variables were compared in patients with and without abnormal ejection fraction responses to exercise by both radionuclide techniques using a t test for the difference of two means.

Results

HAEMODYNAMIC VARIABLES

Table 1 shows the mean changes (±SEM) in heart rate and systolic blood pressure from rest to maximal exercise. The mean workload achieved was 412±30 kpm/min (67·2±4·9 W) and the mean workload per kilogram 9·4±0·5 kpm/kg/min (1·5±0·08 W).

VENTRICULAR FUNCTION

Table 2 gives individual ejection fractions with both techniques at rest and during exercise and the individual workload achieved. For right ventricular ejec-

tion fractions technically satisfactory results were achieved by one or other technique at rest and during exercise in all 25 patients; two first pass results and one equilibrium result were not analysable. For left ventricular ejection fractions 24 of the 25 results were analysable by one or other technique; two first pass and three equilibrium results were technically unsatisfactory. The major technical problem with equilibrium studies was inadequate separation of the right and left ventricular blood pools. The technical problems with first pass studies in individual patients arose from superior vena caval obstruction (two), baffle leak (one), and poor venous access leading to an inadequate technetium 99m bolus (one).

Fig. 1 shows the distribution of resting ejection fractions with both techniques. In the equilibrium studies nine of 24 and in the first pass studies two of 23 right ventricular ejection fractions were below the lower limit of normal; the corresponding figures for left ventricular ejection fractions were eight of 23 and five of 22.

Mean percentage change in right ventricular ejection fraction from rest to maximal exercise is shown in Fig. 2 for both techniques; there was no statistically significant change with maximal exercise in either study. In contrast, mean left ventricular ejection fraction increased significantly with both the equilibrium technique ($p<0·05$) and the first pass technique

Table 2 *Results of ventricular function*

Case No	Right ventricular ejection fraction (%)				Left ventricular ejection fraction (%)				Workload (kpm/kg/min)†
	Equilibrium study		First pass study		Equilibrium study		First pass study		
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	
1	44	57	56	62	49	52	65	62	10·7
2	67	59	*	*	*	*	*	*	9·5
3	*	*	57	58	*	*	57	67	7·1
4	32	48	46	61	51	66	53	69	10·0
5	60	59	55	57	54	53	52	57	5·7
6	49	55	72	65	65	55	66	66	13·0
7	50	39	59	48	66	71	63	75	8·7
8	33	40	55	70	72	76	78	89	5·0
9	57	58	80	76	76	81	78	91	10·8
10	52	59	57	42	95	86	76	79	10·7
11	42	48	46	60	55	66	56	79	13·3
12	38	39	44	42	57	72	62	82	8·1
13	57	52	47	65	53	61	50	61	6·2
14	46	40	38	51	47	51	45	48	13·1
15	43	35	50	48	58	75	*	*	5·9
16	54	48	56	63	51	66	75	73	6·5
17	40	36	55	64	54	52	61	64	8·5
18	44	41	54	54	76	76	65	69	12·2
19	48	39	60	54	58	68	53	·73	8·1
20	44	55	*	*	48	49	*	*	10·2
21	51	49	59	60	73	70	65	78	7·8
22	48	37	52	49	63	54	72	69	6·2
23	61	61	49	53	71	79	62	65	7·3
24	56	41	70	63	84	76	72	77	7·4
25	60	54	62	60	59	81	68	80	10·8
Mean±SEM	49±2	48±2	56±2	58±2	62±2·5	67±2·5	62±2	72±2	9·4±0·5

*Technically unsatisfactory result.
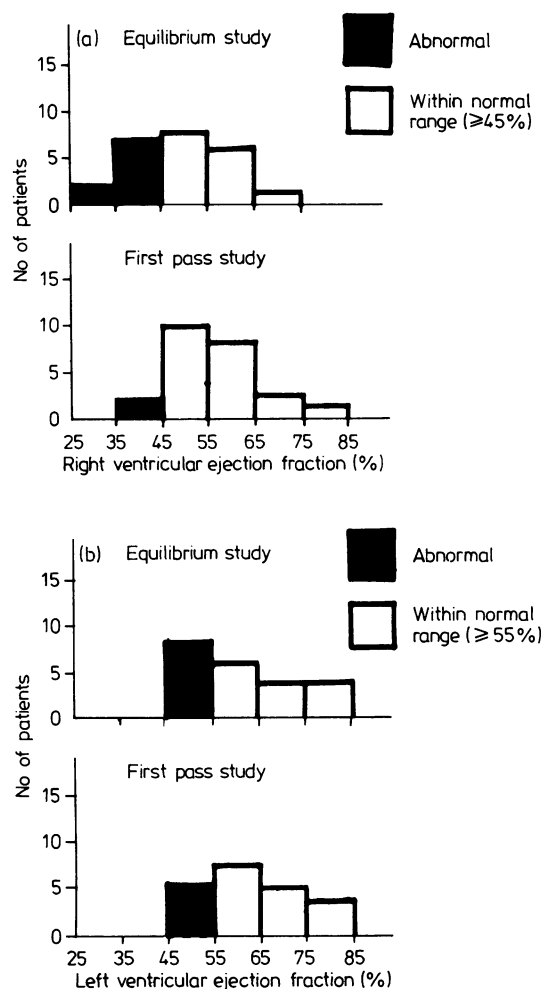†Peak workload/weight.

Fig. 1 *Distribution of resting values for (a) right ventricular ejection fraction and (b) left ventricular ejection fraction obtained by the left anterior oblique equilibrium and right anterior oblique gated first pass techniques.*

(p<0·001) from rest to maximal exercise (Fig. 2b).

Table 3 shows the individual changes in ejection fraction from rest to maximal exercise. Only 29% of patients had a normal right ventricular ejection fraction response to exercise with the equilibrium technique with 71% either having no significant change or having a decrease in ejection fraction >5%; by the first pass technique 39% had a normal and 61% an abnormal response. Fewer patients had abnormal left ventricular ejection fraction responses to exercise; with the equilibrium technique 35% had an abnormal response and with the first pass technique 41% had an abnormal response.

Twenty two patients had technically adequate right ventricular ejection fractions measured by both techniques; only 15 (68%) showed concordant results for the presence or absence of a normal response to exercise (four a normal and 11 an abnormal response). In the 21 patients with technically adequate left ventricular ejection fractions with both techniques, 18 (86%) had concordant results; abnormal responses with both techniques were present in six (28%).

Of the nine patients with abnormal resting right ventricular ejection fractions with the equilibrium technique, five showed a normal response to exercise. Of the two first pass results showing a low resting right ventricular ejection fraction, one showed a normal response to exercise. Of the patients with an abnormal resting left ventricular ejection fraction five of nine and two of five by the equilibrium and first pass techniques respectively had an abnormal response to exercise.

STATISTICAL ANALYSIS

There was no statistically significant difference in age at operation, current age, time since operation, superior vena caval obstruction, presence of arrhythmias, cardiothoracic ratio, heart rate and systolic blood pressure response to exercise, or workload achieved between patients who did or did not have an increase in right ventricular ejection fraction or left ventricular ejection fraction normally during exercise.

Table 3 *Patterns of exercise ejection fraction responses. Values are numbers (%) of patients*

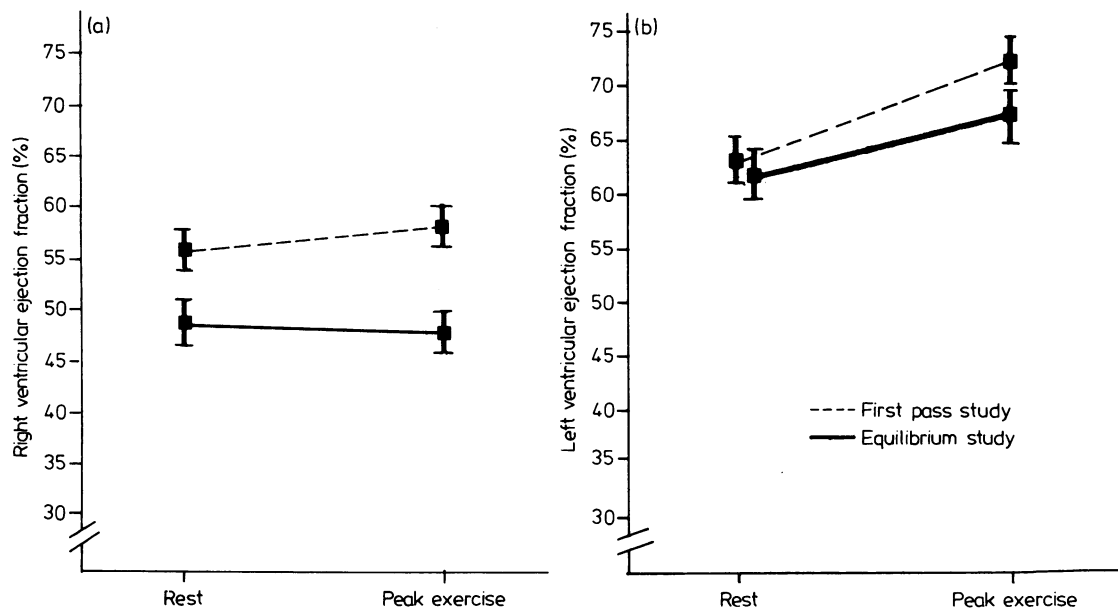|	RV ejection fraction		LV ejection fraction	
Response*	Equilibrium study	First pass study	Equilibrium study	First pass study
Increase (+5%)	7 (29)	9 (39)	15 (65)	13 (59)
No significant change (−5% to +5%)	8 (33)	9 (39)	6 (26)	9 (41)
Decrease (−5%)	9 (38)	5 (22)	2 (9)	0 (0)

*Change from resting values to those during exercise

Fig. 2   Mean (±SEM) values for (a) right ventricular ejection fraction and (b) left ventricular ejection fraction at rest and at maximal exercise obtained by both left anterior oblique equilibrium and right anterior oblique gated first pass techniques.

Discussion

This study has shown abnormalities of both right and left ventricular function at rest and with exercise in a substantial proportion of asymptomatic patients with transposition of the great arteries at a mean of 10·9 years after a Mustard repair. Patients also had a generally lower heart rate and a lower peak systolic blood pressure than has been reported in normal children.[14][15] The mean workload achieved in our study of 9·4±0·5 kpm/kg/min was similar to that of 8·7 kpm/kg/min in a recent comparable study.[16]

The normal range of resting right ventricular ejection fraction in this study was derived from patients with the right ventricle functioning in the pulmonary circuit.[12][13] It is not known whether the same values are valid for the right ventricle when it is the systemic ventricle. Some information on resting right ventricular ejection fraction derived from contrast angiography in congenitally corrected transposition of the great arteries has been reported by Graham et al.[17] Children under 10 years with this condition had right ventricular ejection fractions corresponding closely to those found in normal children.[17]

The significantly lower right ventricular ejection fraction obtained by the equilibrium technique than with the first pass technique (Fig. 2a) is in keeping with other reports,[18] which state that difficulty in

excluding overlapping right atrial activity with the equilibrium technique may lead to underestimation of absolute right ventricular ejection fraction by that method. This limitation does not necessarily prevent either technique providing equally valid methods of measuring right ventricular ejection fraction response to exercise since right atrial activity should remain proportionately the same at rest and exercise.

In this study the ejection fraction measurements were often technically difficult to perform and to analyse. The same observation has recently been made in similar studies by Benson et al,[16] Parrish et al,[19] and Murphy et al.[20] Benson's study began with 35 patients but had only 19 technically analysable results. This difficulty is predominantly related to the large right ventricle making separation of the two ventricles difficult and also to residual haemodynamic problems such as superior vena caval obstruction and baffle leak. In this study the use of both first pass and equilibrium techniques resulted in technically adequate results in all patients by one or other technique. This would not have been possible using either technique alone.

The fundamental assumptions required in radionuclide measurement of right ventricular ejection fraction and the theoretical difficulties in obtaining valid results are greater than for left ventricular ejection fraction measurements.[18] The first pass and

equilibrium techniques each have their own different theoretical drawbacks.[10][11][18] In this study there was an overall concordance between the mean right ventricular ejection fraction and left ventricular ejection fraction responses to exercise and in the proportion of patients who had an abnormal exercise response obtained by both techniques. This would appear to decrease any uncertainty about the validity of these findings which may arise from theoretical drawbacks specific to either technique.

Although the combined use of both techniques in this study increased the yield of technically analysable results and increased the validity of its major conclusions, it also highlighted a major difficulty in the potential application of this information in individual patients. This is because the technical problems in obtaining reliable measurements of right ventricular ejection fraction in individual patients are emphasised by the frequent disagreement between right ventricular ejection fraction exercise responses with the two techniques.

The response of the right ventricle to exercise may provide a more reliable guide to ventricular function and reserve than resting values for right ventricular ejection fraction. Three recent studies[16][19][20] examined ventricular function at rest and with exercise using radionuclide ventriculography postoperatively in patients with transposition of the great arteries. All three studies were performed using equilibrium techniques only. Essentially similar results were found by the other investigators for mean values for right ventricular ejection fraction and response to exercise. There was no significant increase in the mean values with exercise in any of the studies. The proportions of patients having an abnormal response to exercise were closely related, being 11/19 (58%) in Benson *et al*'s study,[16] 6/11 (55%) in Parrish *et al*'s study,[19] and 15/26 (58%) in Murphy *et al*'s.[20]

Resting values for right ventricular ejection fraction were not a reliable guide to whether these values would increase with exercise in our study or in Benson's study.[16] In both our study and Benson's about half of the patients with resting right ventricular ejection fraction <45% had an increase of >5% during exercise. In contrast to these findings Murphy[20] found that a resting right ventricular ejection fraction <45% was a good guide to right ventricular ejection fraction response to exercise, since none of the eight patients in this group had a normal increase in ejection fraction. The findings in our study and Benson's are more similar in this regard to the left ventricular ejection fraction reported in patients with systemic left ventricular dysfunction without transposition of the great arteries.[4]

Murphy *et al* found that those patients performing a high workload were more likely to have a normal increase in right ventricular ejection fraction with exercise.[20] This has not been shown in the studies by Benson[16] or Parrish,[19] and could not be confirmed by the results of this study. The absence of a consistently demonstrable relation between ventricular function and exercise capacity after repair of transposition of the great arteries is in keeping with reports that exercise capacity is not closely related to the severity of left ventricular dysfunction in patients without transposition of the great arteries.[21][22]

Only two of the three other relevant studies examined left ventricular ejection fraction.[19][20] Murphy *et al* found 10/24 (42%) had an abnormal response to exercise[20] whereas Parrish *et al* found a much higher prevalence (10/11 (91%) patients).[19] The fact that our study's results were very similar to those of Murphy by two independent techniques suggests that they may be more representative of the prevalence of exercise induced left ventricular dysfunction in this group of patients.

A relation between an abnormal left ventricular ejection fraction response to exercise and complex ventricular arrhythmias was found by Murphy *et al*. There were, however, only six patients in our study with any ventricular extrasystoles on 24 hour ambulatory monitoring, and four had totally normal left ventricular ejection fraction values both at rest and during exercise.

The finding of ventricular dysfunction in both right and left ventricles points to a generalised problem with the myocardium which is not only related to the right ventricle's ability to cope with a systemic load. It is probable that the aetiology of these abnormalities is multifactorial,[23] and possible mechanisms have been recently reviewed.[24] The anatomical "switch" operation has been recommended as an alternative to a baffle operation for transposition of the great arteries, with the expected benefit of avoiding cardiac failure resulting from continued systemic load on the right ventricle.[3][24] If left ventricular dysfunction is inevitable in an appreciable proportion of children with this defect, then the expected benefits from the "switch" operation may not be achieved.

The children in this study had their operations performed between 1971 and 1974 and at a mean age of 2·6 years. It will not be known for some time whether earlier operation, improved perioperative care, and other advances in cardiac surgery may have reduced the prevalence of late postoperative abnormalities in ventricular function.

At present all of the patients in this study are clinically well. What these abnormalities mean to the future of these patients is unclear. Resting ejection fractions, ejection fraction response to exercise, and absolute exercise values all merit consideration as possible important prognostic indicators. Longitudi-

nal studies need to be carried out to determine whether abnormalities in any of these indices may be related to complications such as sudden death or the development of cardiac failure.

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